Observational Study

Neurogenic Thoracic Outlet Syndrome and other Forms of Cervical Brachial Syndrome Treated with Plasma Concentrate Enriched for Alpha 2 Macroglobulin

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Background: Existing therapies for myofascial and neuralgic forms of cervicobrachial pain may have unsatisfactory outcomes. Alternative therapies may be considered, particularly for individuals who have failed to respond. Contemporary conceptualizations of chronic pain mechanisms include the contribution of inflammatory factors; therefore, locally targeted antiinflammatory administrations may play a role in treatment of cervicobrachial pain.

Alpha 2 macroglobulin (A2M) is a plasma protein that acts as a molecular trap for inflammatory factors such as tumor necrosis factor. After plasma is enriched for A2M, it may be considered as a possible injectable agent to counteract inflammation that may occur with a cervicobrachial pain syndrome.

Objectives: This retrospective review evaluates patient response to the use of plasma concentrate enriched for alpha 2 macroglobulin (A2M-PPP) in treatment of neurogenic thoracic outlet syndrome (TOS) and other forms of cervical brachial syndrome.

Study Design: Observational Study.

Setting: Outpatient interventional neurology practice.

Methods: There were 62 patients, including 46 women and 16 men ages 23-77 years. Twenty-three of these patients were diagnosed with complex regional pain syndrome (CRPS) or fibromyalgia, 18 with TOS, and 21 with musculotendinous pain (MTP). At baseline, 1 month, 3 months, and 6 months, patient status was evaluated with a Brief Pain Inventory (BPI) that included a composite pain score and a functional interference score. Patients were asked to estimate overall satisfaction with a Patient Global Impression of Change (PGIC) scale. Criterion for clinically significant improvement included >30% betterment in the BPI pain and functional interference subscales and a PGIC of > 5 at the 3-month mark.

Results: Three patients, one with CRPS and 2 with TOS, complained of several days of worsened pain or dysesthesias. No serious or permanent complications were encountered. For patients with TOS at the 3-month mark, 61% achieved clinical endpoints of success compared with 35% with CRPS/fibromyalgia and 24% for patients with MTP ($P < 0.05$, chi-square). By 6 months, 22% of individuals in the neuropathic TOS group had > 30% improvements in pain and functional interference scores compared with 13% of the individuals in the CRPS/fibromyalgia group and 18% in the MTP group.

Limitations: This article does not differentiate the added benefit of A2M-PPP from hydrodissection alone. Additionally, this article does not evaluate the actual benefit of the A2M molecule apart from other factors present in the platelet-poor concentrate such as exosomes and cytokines. With the advent of pure engineered A2M, more focused studies will be possible. Also, an independent assay was not done, and therefore we cannot be precisely sure about the exact quantity of platelets, if any, which were contained in the platelet-poor concentration.

Conclusions: Results suggest that A2M-PPP, when injected into muscle, tendon, and epineurium with live ultrasound guidance, appears to be relatively safe and free of postinjection inflammatory reactions that are often seen after platelet-poor plasma injection. A2M-PPP appears to be associated more frequently with good outcomes when injected into brachial plexus targets in patients with TOS compared with outcomes observed after injection of the plexus in patients with CRPS/fibromyalgia.

Key words: Plasma concentrate enriched for alpha 2 macroglobulin, neurogenic thoracic outlet syndrome, cervical brachial syndrome

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Regional pain in the neck, shoulder, and arm is a common problem with a prevalence of about 50% (1-3). In the absence of a widespread pain condition such as fibromyalgia, and when cervical radiculopathy is ruled out with appropriate imaging, muscular or neurogenic sources of pain may predominate in a given case. Musculotendinous pain (MTP), often further specified as myofascial pain, may be characterized by muscles that are tight and tender to palpation, and in which there may be radiation of pain down the limb. A twitch may be elicited with stimulation of the affected muscle (4,5). Numerous treatments for myalgia have been proposed with variable or incomplete success including local anesthetic injections, botulinum chemodenervation, and platelet-poor plasma injections (6-8).

Neuralgic complaints may be caused by chronic compression in the interscalene triangle as in thoracic outlet syndrome (TOS), and other patients may have injury from sudden stretch, electrocution, inflammatory diseases, penetrating wounds, and acute or chronic postoperative conditions. Botulinum chemodenervation and surgical decompression has been applied for treating nerve compression due to TOS with partial success (9-13). Chemodenervation tends to be transient in effect, and surgery may have significant complications.

Previous reports have demonstrated relatively poor outcomes with targeted treatments when there is a coexistence of conditions characterized with increased sensitivity or by widespread pain as in complex regional pain syndrome (CRPS) or fibromyalgia. In the present retrospective review, it was anticipated that patients with CRPS or fibromyalgia may not respond as well to targeted treatment, so that they were evaluated separately from patients with TOS without sensitization.

Because existing therapies for myofascial and neuralgic forms of cervicobrachial pain may have unsatisfactory outcomes, alternative therapies may be considered, particularly for individuals who have failed to respond. Contemporary conceptualizations of chronic pain mechanisms include the contribution of inflammatory factors. Mindful of these considerations, locally targeted antiinflammatory administrations may be thought to play a potential role in treatment of cervicobrachial pain.

Alpha 2 macroglobulin (A2M) is a plasma protein that acts as a molecular trap for inflammatory factors such as tumor necrosis factor (TNF) (14). After plasma is enriched for A2M, it may be injected for treating chronic inflammation (15,16). Plasma enriched for A2M may be considered as a possible injectable agent to counteract inflammation that may occur with a cervicobrachial pain syndrome. The present article reports on an experience using A2M for treating cervicobrachial syndrome, which was predominant for either musculotendinous or neuralgic features.

Methods

All patients were examined by one or both of the physicians (S.J., H.G.) on referral to a university affiliated clinic for evaluating possible TOS. All of the patients provided written informed consent involving the experimental nature of the injections, and the possible risks or benefits of the treatment. A2M-PPP was injected as part of the patients' clinical care after they had failed previous treatments. The patients were not paid for their participation in this study. The present retrospective analysis was approved by the institutional review board. The processing of autologous A2M by the Cytonics APIC system (Cytonics, Jupiter, FL) has 510K clearance by the US Food and Drug Administration.

In the process of examination and treatment, patients had magnetic resonance imaging scans of the cervical spine to evaluate for possible spinal sources of pain. All of the patients had physical therapy, counseling on proper body mechanics and ergonomics, and had appropriate trials of analgesic and antiinflammatory medication. All of the patients had daily disabling cervical brachial pain that was continuously present for at least 6 months. After examination, patients were categorized according to the predominant pain problem: MTP, TOS, or a condition with evidence of widespread pain or sensitization (fibromyalgia or CRPS). Although fibromyalgia and CPRS have distinct clinical phenotypes, they have numerous underlying similarities including but not limited to pain, allodynia, dysesthesias (all occurring in similar ways), often onset following traumas, have many overlapping pathophysiological mechanisms, and have similar peripheral effects (e.g., neurogenic inflammation) that contribute to their clinical manifestation (17). Therefore, given these overlapping qualities, the majority of which may be affected by the mechanistic action of A2M, grouping these patients into a single study group appears to be methodologically sound.

Patients with predominantly muscular sources of pain had tight and tender bands in the levator, scapula, trapezius and/or rhomboid muscles with distal radiation on palpation. Patients in the latter category were placed in the MTP category. Patients categorized

as neuropathic TOS had predominant findings of continual positional-induced dysesthesias in a brachial plexus distribution with effort-dependent limb weakness and dysesthesias. Patients categorized as CRPS had symptoms consistent with neuropathic Thoracic Outlet Syndrome (TOS), but in addition they fulfilled the Budapest Criteria with findings that included combinations of hand swelling without clear evidence of venous occlusion, asymmetrical hand temperature changes measured by infrared thermometry of > 1.5°F, abnormal sweating, trophic changes in nails, skin, or hair growth and/or marked allodynia to light touch or light pressure (18). Patients with fibromyalgia met the widespread pain and symptom severity scoring criteria. MTP patients had injections into the neck and shoulder targets as outlined later.

Both patients with TOS and CRPS/fibromyalgia had injection of the brachial plexus (19). Plasma concentrate enriched for alpha 2 macroglobulin (A2M-PPP) was produced by a centrifugation and filtration process developed by Cytonics Corporation. Initially, 7 mL of Anticoagulant Citrate Dextrose Solution A, USP was drawn into a 60 mL syringe, and then an additional 38 mL of autologous blood was drawn up through an antecubital vein. The supernatant plasma fraction was then transferred to a roller pump system that circulates the fluid through a proprietary filter having a high molecular weight cutoff designed to trap larger molecules including A2M (720 kDa). Performing independent assays to verify the manufacturer's plasma fraction was beyond the scope of this project. Nevertheless, the plasma fraction has been demonstrated to be platelet-poor by the manufacturer based on their spin rate of 4,000 rpm (1,280G) for 4 minutes, which separates out cellular elements including platelets (Cytonics Corporation, https://cytonics.com).

In patients with MTP, each patient had live ultrasound-guided injection with a 25-gauge needle of 2 mL of A2M-PPP injectant in each muscle split between tendon insertions, into tender band-like areas of the muscles, into additional tender points, and adjacent to areas of increased signal on power Doppler. A 10-MHz ultrasound probe was used during needle insertion and during injection. Every patient had a target set that included levator scapula, trapezius, rhomboid, and cervical paraspinals.

For patients with TOS and CRPS/fibromyalgia, the lower, middle, and upper brachial plexus trunks were targeted with 25-gauge needles, and the epineural space was injected first with 5 to 10 mL of saline solution split between these sites with 400 units of hyaluronidase to develop a plane adjacent to the neural elements, and 4 mL of A2M-PPP was injected.

At baseline and at one month, 3 months, and 6 months, patient status was evaluated with a Brief Pain Inventory (BPI) that included a composite pain score and a functional interference score, and patients were asked to estimate overall satisfaction with a Patient Global Impression of Change (PGIC) scale.

For the purposes of establishing a clinically significant improvement, each patient was scored as a success if there was at least a 30% improvement (20) in both the BPI pain subscale and functional interference subscale and a PGIC of 5 or better at the 3-month mark.

Results

There were 62 patients in the 3 groups, with 46 women and 16 men with an age range of 23 to 77 years. Twenty-three were diagnosed with CRPS or fibromyalgia. Eighteen were diagnosed with TOS, and the remaining 21 were diagnosed with MTP. Eight of the patients with CRPS/fibromyalgia had a thoracic outlet decompression surgery, 12 of the patients with TOS had prior surgery.

There were 3 patients, one with CRPS and 2 with TOS, who complained of several days of worsened pain or dysesthesias. No serious or permanent complications were encountered. For patients with TOS at the 3-month mark, 11 of 18 (61%) achieved clinical endpoints of success compared with 6 of 23 (35%) with CRPS/fibromyalgia, and 4 of 17 (24%) for patients with MTP ($P < 0.05$, chi-square). By 6 months, there were 4 individuals (22%) in the TOS group that had at least 30% improvements in pain and functional interference scores compared with 3 individuals in the CRPS/fibromyalgia group (13%) and 3 in the MFP group (18%). Therefore, the TOS group displayed the greatest clinical success at 3 months posttreatment and maintained the largest ongoing improvement in symptoms at 6 months posttreatment of the 3 groups.

Discussion

According to the results of the present study, A2M-PPP when injected into muscle, tendon, and epineurium with live ultrasound guidance appears to be relatively safe and relatively free of postinjection inflammatory reactions that are often seen after leukocyte-rich platelet-poor plasma injection. A2M-PPP appears to be associated more frequently with good outcomes when injected into brachial plexus targets in patients with

TOS as compared with outcomes observed after injection of the plexus in patients with CRPS or fibromyalgia. Our findings are in-line with those recently reported in degenerative disc disease patients (21).

Injection for muscle and tendon targets does not appear to be as likely to yield good outcomes in patients with MTP. Targeting the precise pain generator may be problematic in these patients. A2M is a large molecule and it would appear probable that diffusion from sites of injection may be limited so that precise localization is probably critical, as it is with administration of other commonly used large molecules (e.g., articulate forms of steroid), which demonstrate similar properties including difficulty diffusing far distances beyond the local injection site. In the present study, targeting was based on finding a palpable tender nodule, finding other tender areas, and looking for vascular signal with power Doppler. The presently used targeting protocol may not be sufficiently precise.

Perhaps more advanced targeting with ultrasonic elastography may yield better results. Poor diffusion is not likely to be a limiting factor with epineural injection as in patients treated for TOS because there is direct deposition of A2M-PPP next to the affected nerve in the interscalene triangle. As expected with similar interventions in the past, patients with increased sensitivity, as in CRPS or fibromyalgia, do not fare as well as patients with lessor degrees of sensitization (10).

Although hyaluronidase was administered to patients with CRPS did not do well. Therefore, it is unlikely that hyaluronidase is responsible for the improvement seen in either the fibromyalgia group, who did receive hyaluronidase, or the MTP group, who did not receive hyaluronidase.

The ongoing improvement in symptoms, in the 3- to 6-month time frame, is not unexpected because inflammation caused by recurrent adhesions or reinstitution of compression and traction of plexus elements is not prevented as the persistence of A2M gradually dissipates over time. The response is similar to those results encountered with knee injection with A2M-PPP (22). In this manner, A2M-PPP may be considered a relatively safe and temporary treatment for symptoms related to TOS as an alternative to injections that include steroids or repeat surgical decompression and neurolysis. The mechanism of action of A2M is likely via protease inhibition throughout various tissue media via inhibition of proinflammatory cytokines (e.g., TNF-alpha, interleukin-1-beta), inflammatory proteases, and matrix metalloproteinases (cathepsin, elastase). A2M has also been shown to slow cartilage degeneration through enhanced activities of catabolic enzymes (23).

Conclusions

A limitation of this article is that it does not sort out the added benefit of A2M-PPP in comparison to hydrodissection alone. Additionally, this article does not sort out the actual benefit of the A2M molecule in comparison with other factors present in the platelet-poor concentrate such as exosomes and cytokines. With the advent of pure engineered A2M, more focused studies will be possible in the future. Also, an independent assay was not done, and therefore we cannot be precisely sure about the exact quantity of platelets, if any, which were contained in the platelet-poor concentration. Based on the centrifugation parameters, the likelihood is that our solution was similar to those assays on the market, and therefore it is unlikely that many platelets would remain in the supernatant.

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